



## Drug Enforcement Administration

### 21 CFR Part 1308

[Docket No. DEA-371]

#### Schedules of Controlled Substances: Placement of Amineptine in Schedule I

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Drug Enforcement Administration proposes placing the substance amineptine (chemical name: 7-[(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)amino]heptanoic acid), including its salts, isomers, and salts of isomers, in schedule I of the Controlled Substances Act. This action is being taken to enable the United States to meet its obligations under the 1971 United Nations Convention on Psychotropic Substances. If finalized, this action would impose the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle, amineptine.

**DATES:** Comments must be submitted electronically or postmarked, on or before [INSERT DATE 60 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Interested persons may file a request for hearing or waiver of hearing pursuant to 21 CFR 1308.44 and in accordance with 21 CFR 1316.45 and/or 1316.47, as applicable. Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing, together with a written statement of position on the matters of fact and law asserted in the hearing, must be received on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

**ADDRESSES:** Interested persons may file written comments on this proposal in accordance with 21 CFR 1308.43(g). The electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference “Docket No. DEA-371” on all electronic and written correspondence, including any attachments.

- *Electronic comments:* DEA encourages commenters to submit all comments electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the webpage or attach a file for lengthier comments. Please go to <http://www.regulations.gov> and follow the on-line instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number. Submitted comments are not instantaneously available for public view on <http://www.regulations.gov>. If you have received a Comment Tracking Number, you have submitted your comment successfully, and there is no need to resubmit the same comment.
- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary and are discouraged. Should you wish to mail a paper comment in lieu of an electronic comment, send via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.
- *Hearing requests:* All requests for a hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrisette Drive, Springfield, Virginia 22152. All requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/LJ, 8701 Morrisette Drive, Springfield, Virginia 22152; and (2) Drug

Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.

**FOR FURTHER INFORMATION CONTACT:** Terrence L. Boos, Drug & Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

**SUPPLEMENTARY INFORMATION:**

**Posting of Public Comments**

All comments received in response to this docket are considered part of the public record. The Drug Enforcement Administration (DEA) will make comments available, unless reasonable cause is given, for public inspection online at <http://www.regulations.gov>. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want DEA to make it publicly available, you must include the phrase “PERSONAL IDENTIFYING INFORMATION” in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want DEA to make it publicly available, you must include the phrase “CONFIDENTIAL BUSINESS INFORMATION” in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

DEA will generally make available in publicly redacted form comments containing personal identifying information and confidential business information

identified as directed above. If a comment has so much confidential business information that DEA cannot effectively redact it, DEA may not make available publicly all or part of that comment. Comments posted to <http://www.regulations.gov> may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as confidential as directed above.

An electronic copy of this document and supplemental information to this proposed rule are available at <http://www.regulations.gov> for easy reference.

### **Request for Hearing or Appearance; Waiver**

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking “on the record after opportunity for a hearing.” Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act, 5 U.S.C. 551–559. 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D. Interested persons may file requests for a hearing or notices of intent to participate in a hearing in conformity with the requirements of 21 CFR 1308.44(a) or (b), and they shall include a statement of interest in the proceeding and the objections or issues, if any, concerning which the person desires to be heard. 21 CFR 1316.47(a). Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing together with a written statement regarding the interested person’s position on the matters of fact and law involved in any hearing as set forth in 21 CFR 1308.44(c).

All requests for hearing and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above.

### **Legal Authority**

The United States is a party to the 1971 United Nations Convention on Psychotropic Substances (1971 Convention), February 21, 1971, 32 U.S.T. 543, 1019

U.N.T.S. 175, as amended. Procedures respecting changes in drug schedules under the 1971 Convention are governed domestically by 21 U.S.C. 811(d)(2-4). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention indicating that a drug or other substance has been added to a schedule specified in the notification, the Secretary of the Department of Health and Human Services (HHS),<sup>1</sup> after consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act meet the requirements of the schedule specified in the notification with respect to the specific drug or substance.

21 U.S.C. 811(d)(3). In the event that the Secretary of HHS (Secretary) did not consult with the Attorney General, and the Attorney General did not issue a temporary order, as provided under 21 U.S.C. 811(d)(4), the procedures for permanent scheduling set forth in 21 U.S.C. 811(a) and (b) control. Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may add to such a schedule any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes the findings prescribed by 21 U.S.C. 812(b) for the schedule in which such drug is to be placed. The Attorney General has delegated this scheduling authority to the Administrator of DEA. 28 CFR 0.100.

## **Background**

Amineptine is a synthetic tricyclic antidepressant with central nervous system (CNS) stimulating properties that, according to HHS, has no approved medical use and no known therapeutic application in the United States. Pharmacological studies indicate that amineptine's primary mode of action is to increase extracellular levels of dopamine

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<sup>1</sup> As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the Controlled Substances Act, with the concurrence of NIDA. 50 FR 9518 (March 8, 1985). The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460 (July 1, 1993).

and norepinephrine as well as inhibit re-uptake of dopamine and norepinephrine within the striatum and limbic areas of the brain.

In 1978, amineptine was approved for use in France as an antidepressant and subsequently marketed in 66 countries throughout Africa, Asia, Europe, and South America. As documented by the World Health Organization's (WHO) Expert Committee on Drug Dependence in its 33<sup>rd</sup> report (2003) (WHO 2003 report), amineptine has been withdrawn from the market in 49 of the 66 countries. The status of current production of amineptine in other countries is not known, although a small quantity is most likely produced for research purposes.

In April 2003, the United Nations Commission on Narcotic Drugs, on the advice of the Director-General of the WHO, added amineptine to Schedule II of the 1971 Convention, thus notifying all parties to the 1971 Convention.<sup>2</sup> Because the procedures in 21 U.S.C. 811(d)(3) and (4) for consultation and issuance of a temporary order for amineptine, discussed in the above legal authority section, were not followed, DEA is utilizing the procedures for permanent scheduling set forth in 21 U.S.C. 811(a) and (b) to control amineptine. Such scheduling would satisfy the United States' international obligations.

Article 2, paragraph 7(b), of the 1971 Convention sets forth the minimum requirements that the United States must meet when a substance has been added to Schedule II of the 1971 Convention. Pursuant to the 1971 Convention, the United States must require licenses for the manufacture, export and import, and distribution of amineptine. This license requirement is accomplished by the CSA's registration requirement as set forth in 21 U.S.C. 822, 823, 957, 958 and in accordance with 21 CFR parts 1301 and 1312. In addition, the United States must adhere to specific export and import provisions set forth in the 1971 Convention. This requirement is accomplished by

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<sup>2</sup> [https://www.unodc.org/unodc/en/Resolutions/resolution\\_2003-04-08\\_1.html](https://www.unodc.org/unodc/en/Resolutions/resolution_2003-04-08_1.html).

the CSA's export and import provisions established in 21 U.S.C. 952, 953, 957, 958 and in accordance with 21 CFR part 1312. Likewise, under Article 13, paragraphs 1 and 2, of the 1971 Convention, a party to the 1971 Convention may notify through the UN Secretary-General another party that it prohibits the importation of a substance in Schedule II, III, or IV of the 1971 Convention. If such notice is presented to the United States, the United States shall take measures to ensure that the named substance is not exported to the notifying country. This requirement is also accomplished by the CSA's export provisions mentioned above. Under Article 16, paragraph 4, of the 1971 Convention, the United States is required to provide annual statistical reports to the International Narcotics Control Board (INCB). Using INCB Form P, the United States shall provide the following information: (1) in regard to each substance in Schedule I and II of the 1971 Convention, quantities manufactured in, exported to, and imported from each country or region as well as stocks held by manufacturers; (2) in regard to each substance in Schedule II and III of the 1971 Convention, quantities used in the manufacture of exempt preparations; and (3) in regard to each substance in Schedule II - IV of the 1971 Convention, quantities used for the manufacture of non-psychoactive substances or products. Lastly, under Article 2 of the 1971 Convention, the United States must adopt measures in accordance with Article 22 to address violations of any statutes or regulations that are adopted pursuant to its obligations under the 1971 Convention. Persons acting outside the legal framework established by the CSA are subject to administrative, civil, and/or criminal action; therefore, the United States complies with this provision.

DEA notes that there are differences between the schedules of substances in the 1971 Convention and the CSA. The CSA has five schedules (schedules I-V) with specific criteria set forth for each schedule. Schedule I is the only possible schedule in which a drug or other substance may be placed if it has high potential for abuse and no

currently accepted medical use in treatment in the United States. See 21 U.S.C. 812(b). In contrast, the 1971 Convention has four schedules (Schedules I-IV) but does not have specific criteria for each schedule. The 1971 Convention simply defines its four schedules, in Article 1, to mean the correspondingly numbered lists of psychotropic substances annexed to the Convention, and altered in accordance with Article 2.

### **Proposed Determination to Schedule Amineptine**

Pursuant to 21 U.S.C. 811(b), DEA gathered the necessary data on amineptine and, on August 12, 2008, submitted it to the Assistant Secretary for Health of HHS with a request for a scientific and medical evaluation of available information and a scheduling recommendation for amineptine. On November 8, 2011, HHS provided to DEA a written scientific and medical evaluation and scheduling recommendation entitled “Basis for the Recommendation for Control of Amineptine in Schedule I of the Controlled Substances Act.” In this recommendation, HHS presented its eight-factor analysis as required under 21 U.S.C. 811(b) and recommended that amineptine be added to schedule I of the CSA.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS and all other relevant data and conducted its own eight-factor analysis pursuant to 21 U.S.C. 811(c). Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in the scheduling decision. Both DEA and HHS analyses are available in their entirety under “Supporting and Related Material” of the public docket for this rule at <http://www.regulations.gov> under docket number DEA-371.

*1. The Drug’s Actual or Relative Potential for Abuse:* As reported by HHS, the WHO 2003 report showed strong evidence of abuse in Europe and Asia, where amineptine was approved for use as an antidepressant. Additional HHS findings showed that due to reports of hepatotoxicity and abuse in Europe, Servier (a French pharmaceutical company) voluntarily discontinued the French marketing authorization in



France and Spain for amineptine in 1999 (HHS, 2011<sup>3</sup>; WHO, 2002<sup>4</sup>). However, as documented by the WHO 2003 report, the medical use of amineptine and its abuse in developing countries still existed during 1990 to 2003. Clinical studies used between 100 – 200 mg of amineptine (Lachatre et al., 1989<sup>5</sup>; Sbarra et al., 1981<sup>6</sup>); however, case reports from various countries (none in the United States due to its lack of approved medical use or known therapeutic application in the United States) have reported hospitalizations due to amineptine abuse and overdose following the ingestion of 2,000 – 4,300 mg and even up to 12 g daily. However, adverse effects at prescribed doses of amineptine were still observed (see Factor 6).

Evidence shows that amineptine produces behavioral effects in humans and animals that are similar to amphetamine and cocaine (both in schedule II).

Pharmacological studies have demonstrated that amineptine has reinforcing effects as shown by the self-administration test and has locomotor stimulant effects. Studies also have shown that amineptine increases extracellular concentrations of dopamine in the brain, particularly in the striatum and nucleus accumbens, which are structures constituting the reward pathway and are known to be involved in the abuse of drugs, including amphetamine and cocaine. The above data indicate that amineptine has the potential for abuse similar to other CNS stimulants controlled under the CSA, such as cocaine and amphetamine.

*2. Scientific Evidence of the Drug's Pharmacological Effects, if Known:* As stated by HHS, amineptine increases dopamine levels by inducing the synaptosomal

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<sup>3</sup> Health and Human Services (HHS) (2011). Basis for the Recommendation for Control of Amineptine in Schedule I of the Controlled Substances Act.

<sup>4</sup> WHO's Critical Review of Psychoactive Substances prepared for evaluation by the 33rd Meeting of the WHO Expert Committee on Drug Dependence held in September, in Annex, 2002.1-14.

<sup>5</sup> Lachatre, G., Piva, C., Riche, C., Dumont, D., Defrance, R., Mocaer, E., Nicot, G. (1989). Single-dose pharmacokinetics of amineptine and of its main metabolite in healthy young adults. *Fundamental and Clinical Pharmacology*, 3(1):19-26.

<sup>6</sup> Sbarra, C., Castelli, M. G., Noseda, A., Fanelli, R. (1981). Pharmacokinetics of amineptine in man. *European Journal of Drug Metabolism and Pharmacokinetics*, 6(2), 123–126.

release and inhibition of dopamine re-uptake and, to a lesser extent, increasing norepinephrine levels, a mode of action mechanistically similar to the known schedule II CNS stimulants amphetamine and cocaine. Animal behavioral studies have shown that amineptine, in addition to its CNS stimulant properties, has anti-depressant, locomotor, and anti-narcoleptic activities. Human behavioral studies have demonstrated that amineptine works similarly to other antidepressants, often with an earlier onset of therapeutic effects. Studies have shown that amineptine administration lowers depression rating scales in patients and results in a positive subjective quality of sleep and subsequent increase in attention and concentration upon waking.

### *3. The State of Current Scientific Knowledge Regarding the Drug or Other*

*Substance:* The chemical name of amineptine is 7-[(10,11-dihydro-5H-dibenzo[*a,d*]cyclohepten-5-yl)amino]heptanoic acid. It is a white, crystalline powder and is soluble in water and in methanol. Humans rapidly absorb amineptine after oral administration, with mean peak plasma concentrations of amineptine and its main metabolite occurring at 1 hour and 1.5 hours, respectively. Amineptine is metabolized in the liver and rapidly excreted and eliminated through the kidneys with mean half-lives of 0.8 hours for amineptine and 2.5 hours for its metabolite. In humans, 70-75 percent of the administered dose of amineptine was excreted in the urine within 48 hours, with most of the elimination occurring within the first 12 hours.

Distribution of <sup>14</sup>C-amineptine was also evaluated in the *Macaca fascicularis* monkey using whole body autoradiography. Results demonstrated high levels of radio-labeled amineptine in the liver and kidneys, with lower levels of activity in the blood, gastrointestinal tract and spleen. In the brain, radioactivity was observed in the cortex, putamen, caudate nucleus, globus pallidus, pulvinar, and geniculate bodies, with lower levels noted in the hippocampus, substantia nigra, and medulla.

4. *Its History and Current Pattern of Abuse:* As mentioned by HHS, there are numerous published reports of amineptine abuse, including 186 cases of abuse between 1978 and 1988 reported to the Regional Centers of Pharmacovigilance and the Laboratory Euthérapie in France, and 65 cases of abuse between 1990 and 1998 appearing in the Observation of Illegal Drugs and Misuse of Psychotropic Medications database. Notably, amineptine has not been approved for medical use in the United States nor is there any documented abuse in the United States of amineptine.

At the 16<sup>th</sup> French Pharmacovigilance meeting in November 1994, the Fernand Widal Pharmacovigilance Centre reviewed 565 cases of amineptine “overconsumption” from 1978 to 1993, and reported multiple characteristics of amineptine abuse including: (1) amineptine abusers typically had a history of alcoholism, drug abuse, and/or eating disorders; (2) 28 percent of the cases of amineptine abuse resulted in neuropsychiatric disorders; (3) 11 percent of patients developed acne-like lesions from amineptine use; (4) withdrawal from amineptine abuse was described as extremely difficult; (5) only 30 percent were abstinent after one month of withdrawal and long-term abstinence was uncommon; and (6) most patients obtained amineptine from pharmacists by prescription theft or by fraudulent prescriptions. Collectively, these three reports show that there has been a continued pattern of abuse from 1978 to 1998.

DEA noted that in the WHO 2003 report, the WHO’s Expert Committee on Drug Dependence stated that the degree of risk to public health associated with the abuse liability of amineptine is substantial, while noting several adverse effects including hepatotoxicity, severe acne, and anxiety. The committee also noted the limited therapeutic usefulness of amineptine due to the availability of safer antidepressants.

Queries of DEA's System to Retrieve Information from Drug Evidence (STRIDE)/STARLiMS<sup>7</sup> and the National Forensic Laboratory Information System (NFLIS)<sup>8</sup> databases on November 17, 2020, did not generate any reports of amineptine, suggesting that it is not trafficked in the United States.

5. *The Scope, Duration, and Significance of Abuse:* According to the published case reports from 1984 to 2001 in France, Italy, Pakistan, Singapore, and Spain, the majority of the reported cases of amineptine abuse involved patients who were prescribed amineptine for an affective disorder. In these cases, abuse normally began one year after amineptine was prescribed for the treatment of depression by patients independently increasing their dosage, especially in those with a history of alcoholism, intravenous drug abuse, and eating disorders.

Amineptine abuse appears to be due to its psychostimulant effect. Indeed, reasons cited for its abuse were increased energy, joy, work output, alertness, and psychomotor performance. Presently, although Internet searches result in Web sites with purported amineptine for sale, these sites do not list the formulation, purity, price, and quantity for this purported amineptine. In addition, the 1971 Convention currently controls amineptine internationally as a Schedule II substance. Amineptine is also controlled in Belgium, Canada, the Czech Republic, Denmark, Estonia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Slovenia, and Sweden.

6. *What, if Any, Risk There is to the Public Health:* As reported by HHS, there are no known fatalities resulting from amineptine use or abuse. Some of the main public health risks of amineptine are related to its serious adverse effects, such as hepatotoxicity,

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<sup>7</sup> STRIDE is a database of drug exhibits sent to DEA laboratories for analysis. Exhibits from the database are from DEA, other federal agencies, and law enforcement agencies. On October 1, 2014, STARLiMS replaced STRIDE as DEA laboratory drug evidence data system of record.

<sup>8</sup> NFLIS is a national drug forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by state and local forensic laboratories across the country. The NFLIS participation rate, defined as the percentage of the national drug caseload represented by laboratories that have joined NFLIS, is over 97%. NFLIS includes drug chemistry results from completed analyses only.

severe acne, and gastrointestinal (acute pancreatitis) effects. In addition, neuropsychiatric symptoms including anxiety, insomnia, nervousness, irritability, dysarthria, acute psychosis, delusions, hallucinations, anorexia, agitation, psychotic disorders, and confusion have resulted from abuse of amineptine.

*7. Its Psychic or Physiological Dependence Liability:* HHS stated that amineptine has been shown to produce physical and psychological dependence as supported by clinical evidence. While amineptine has no clearly defined withdrawal syndrome, reports of withdrawal symptoms include anxiety, dysphoria, nausea, brief psychotic episodes, tremor, psychomotor agitation, somatic symptoms, and sleep disturbances. In addition, a strong desire to take amineptine was noted in individuals upon withdrawal of the drug, a typical characteristic of psychological dependence.

*8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled under the CSA:* DEA and HHS find that amineptine is not an immediate precursor of a substance already controlled under the CSA.

*Conclusion:* Based on consideration of the scientific and medical evaluation and accompanying recommendation of HHS, and based on DEA's consideration of its own eight-factor analysis, DEA finds that these facts and all relevant data constitute substantial evidence of potential for abuse of amineptine. As such, DEA hereby proposes to schedule amineptine as a controlled substance under the CSA.

### **Proposed Determination of Appropriate Schedule**

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V. The CSA outlines the findings required to place a drug or other substance in any particular schedule. 21 U.S.C. 812(b). After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b)(1), finds that:

(1) Amineptine has a high potential for abuse. Amineptine has stimulant and euphoric effects similar to cocaine and amphetamine, which are both schedule II drugs. Amineptine has a high potential for abuse that is equivalent to cocaine and amphetamine and has been abused throughout Europe and Asia.

(2) Amineptine has no currently accepted medical use in treatment in the United States. There are no approved New Drug Applications for amineptine and no known therapeutic application for amineptine in the United States. Therefore, amineptine has no currently accepted medical use in treatment in the United States.<sup>9</sup>

(3) There is a lack of accepted safety for use of amineptine under medical supervision. Clinical experience showed that patients taking amineptine under medical supervision for depression misused and abused the drug by stealing or falsifying prescriptions and taking doses that were 10 to 20 times higher than prescribed. As a result of taking higher doses, many patients developed hepatic, gastrointestinal, cardiovascular, and psychiatric side effects. Amineptine was once marketed in 66 countries throughout Europe, Africa, Asia, and South America. However, amineptine was later withdrawn from the majority of countries due to its abuse potential and lack of safety. Therefore, there is a lack of accepted safety for the use of amineptine under medical supervision.

Although the first finding shows amineptine to have similar effects to schedule II substances such as cocaine and amphetamine, it bears reiterating that there is only one possible schedule in the CSA – schedule I – to place amineptine since it has no currently

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<sup>9</sup> Although there is no evidence suggesting that amineptine has a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by FDA, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated: i. the drug's chemistry must be known and reproducible; ii. there must be adequate safety studies; iii. there must be adequate and well-controlled studies proving efficacy; iv. the drug must be accepted by qualified experts; and v. the scientific evidence must be widely available. 57 FR 10499 (1992), *pet. for rev. denied*, *Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131, 1135 (D.C. Cir. 1994).

accepted medical use in treatment in the United States. See the background section for additional discussion.

Based on these findings, the Administrator of DEA concludes that amineptine warrants control in schedule I of the CSA. 21 U.S.C. 812(b)(1). More precisely, because of its stimulant effects, DEA proposes placing substance amineptine, including its salts, isomers, and salts of isomers, in 21 CFR 1308.11(f) (the stimulants category of schedule I).

### **Requirements for Handling Amineptine**

If this rule is finalized as proposed, amineptine would be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, reverse distribution, import, export, engagement in research, conduct of instructional activities or chemical analysis with, and possession of schedule I controlled substances, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) amineptine, or who desires to handle amineptine, would need to be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, 958 and in accordance with 21 CFR parts 1301 and 1312 as of the effective date of a final scheduling action. Any person who currently handles amineptine and is not registered with DEA would need to submit an application for registration and may not continue to handle amineptine as of the effective date of a final scheduling action, unless DEA has approved that application for registration pursuant to 21 U.S.C. 822, 823, 957, 958 and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person who does not desire or is not able to obtain a schedule I registration would be required to surrender or to transfer all quantities of currently held amineptine to a person registered with DEA before the effective date of

a final scheduling action in accordance with all applicable Federal, State, local, and tribal laws. As of the effective date of a final scheduling action, amineptine would be required to be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable Federal, State, local, and tribal laws.

3. *Security.* Amineptine would be subject to schedule I security requirements and would need to be handled and stored pursuant to 21 U.S.C. 821 and 823 and in accordance with 21 CFR 1301.71–1301.93, as of the effective date of a final scheduling action. Non-practitioners handling amineptine would also need to comply with the employee screening requirements of 21 CFR 1301.90 -1301.93.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of amineptine would need to be in compliance with 21 U.S.C. 825 and 958(e) and in accordance with 21 CFR part 1302, as of the effective date of a final scheduling action.

5. *Quota.* Only registered manufacturers would be permitted to manufacture amineptine in accordance with a quota assigned pursuant to 21 U.S.C. 826 and in accordance with 21 CFR part 1303, as of the effective date of a final scheduling action.

6. *Inventory.* Every DEA registrant who possesses any quantity of amineptine on the effective date of a final scheduling action would be required to take an inventory of amineptine on hand at that time, pursuant to 21 U.S.C. 827 and 958 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (d).

Any person who becomes registered with DEA on or after the effective date of the final scheduling action would be required to take an initial inventory of all stocks of controlled substances (including amineptine) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and 958 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b).



After the initial inventory, every DEA registrant would be required to take a new inventory of all controlled substances (including amineptine) on hand every two years, pursuant to 21 U.S.C. 827 and 958 and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

7. *Records and Reports.* Every DEA registrant would be required to maintain records and submit reports for amineptine, or products containing amineptine, pursuant to 21 U.S.C. 827 and 958 and in accordance with 21 CFR parts 1304, 1312, and 1317, as of the effective date of a final scheduling action. Manufacturers and distributors would be required to submit reports regarding amineptine to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312, as of the effective date of a final scheduling action.

8. *Order Forms.* Every DEA registrant who distributes amineptine would be required to comply with order form requirements, pursuant to 21 U.S.C. 828 and in accordance with 21 CFR part 1305, as of the effective date of a final scheduling action.

9. *Importation and Exportation.* All importation and exportation of amineptine would need to be in compliance with 21 U.S.C. 952, 953, 957, and 958 and in accordance with 21 CFR part 1312 as of the effective date of a final scheduling action.

10. *Liability.* Any activity involving amineptine not authorized by, or in violation of, the CSA or its implementing regulations, would be unlawful and may subject the person to administrative, civil, and/or criminal sanctions.

## **Regulatory Analyses**

*Executive Orders 12866 and 13563, Regulatory Planning and Review, and Improving Regulation and Regulatory Review.*

In accordance with 21 U.S.C. 811(a), this proposed scheduling action is subject to formal rulemaking procedures performed “on the record after opportunity for a hearing,” which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets

forth procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget pursuant to Section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

*Executive Order 12988, Civil Justice Reform*

This proposed regulation meets the applicable standards set forth in Sections 3(a) and 3(b)(2) of E.O. 12988, Civil Justice Reform, to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

*Executive Order 13132, Federalism*

This proposed rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

*Executive Order 13175, Consultation and Coordination with Indian Tribal Governments*

This proposed rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

*Paperwork Reduction Act of 1995*

This action does not impose a new collection of information requirement under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3521).

*Regulatory Flexibility Act*

The Administrator of DEA, in accordance with the Regulatory Flexibility Act, 5 U.S.C. 601-612, has reviewed this proposed rule and, by approving it, certifies that it will not have a significant economic impact on a substantial number of small entities.

DEA proposes placing the substance amineptine, including its isomers, salts, and salts of isomers, in schedule I of the CSA. This action is being taken to enable the United States to meet its obligations under the 1971 Convention. If finalized, this action would impose the regulatory controls and administrative, civil, and/or criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle, amineptine.

According to HHS, amineptine has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision. DEA's research confirms that there is no commercial market for amineptine in the United States. Additionally, queries of DEA's STRIDE/STARLiMS and the NFLIS databases on November 17, 2020, did not generate any reports of amineptine, suggesting that it is not trafficked in the United States. Therefore, DEA estimates that no United States entity currently handles amineptine and does not expect any United States entity to handle amineptine in the foreseeable future. DEA concludes that no United States entity would be affected by this rule, if finalized. As such, the proposed rule will not have a significant effect on a substantial number of small entities.

#### *Unfunded Mandates Reform Act of 1995*

On the basis of information contained in the "Regulatory Flexibility Act" section above, DEA has determined pursuant to the Unfunded Mandates Reform Act (UMRA) of 1995 (2 U.S.C. 1501 *et seq.*) that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any 1 year \* \* \*." Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of the UMRA of 1995.

## List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is proposed to be amended to read as follows:

### **PART 1308— SCHEDULES OF CONTROLLED SUBSTANCES**

1. The authority citation for 21 CFR part 1308 continues to read as follows:

**Authority:** 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

2. Amend § 1308.11 by re-designating paragraphs (f)(1) through (f)(9) as paragraphs (f)(2) through (f)(10), and adding a new paragraph (f)(1) to read as follows:

#### **§ 1308.11 Schedule I.**

\* \* \* \* \*

(f) \* \* \*

(1) Amineptine (7-[(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)amino]heptanoic acid)..... 1219

\* \* \* \* \*

**Anne Milgram,**  
*Administrator.*

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